

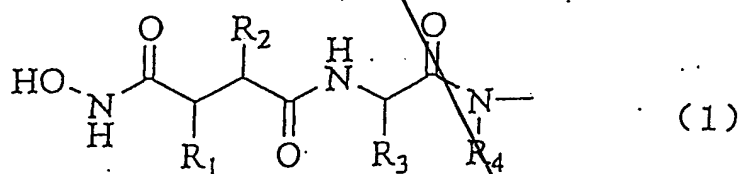
hyaluronic acid, a hyaluronic acid derivative or a salt thereof is a covalent bond.

4. The conjugate of claim 3, wherein the matrix metalloprotease inhibitor binds to hyaluronic acid, a hyaluronic acid derivative or the salt thereof via a spacer.

5. The conjugate of claim 3, wherein the weight ratio of the matrix metalloprotease inhibitor to the entire conjugate is 0.01 to 50%.

6. The conjugate of claim 3, wherein the matrix metalloprotease inhibitor is a hydroxamic acid residue.

7. The conjugate of claim 3, wherein the matrix metalloprotease inhibitor is a hydroxamic acid residue represented by the general formula (1):



wherein

$R_1$  is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;



$R_2$  is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

$R_3$  is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group; and

$R_4$  is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms.

8. The conjugate of claim 4, wherein the spacer is represented by the general formula (2):



wherein

$R_5$  is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;

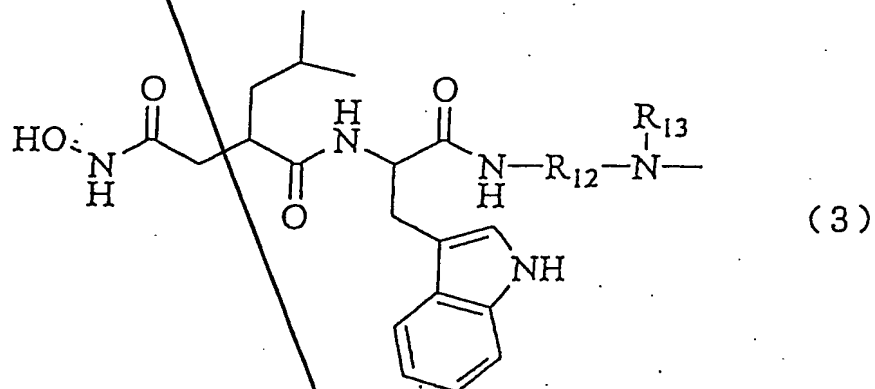
$R_6$  is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

$R_7$  is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and

$R_8$  is an oxygen atom, a sulfur atom or  $NR_9$  wherein  $R_9$  is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms.



9. The conjugate of claim 4, wherein the conjugate of the matrix metalloprotease inhibitor and the spacer is represented by the general formula (3):



wherein

*hm*  
R<sub>12</sub> is a straight-chain or branched-chain alkylene group having 2 to 23 carbon atoms into which one imino group and/or one to four oxygen atoms may be inserted; and

R<sub>13</sub> is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms.

10. The conjugate of claim 3, wherein the matrix metalloprotease inhibitor in the form of a conjugate with hyaluronic acid, a hyaluronic acid derivative or a salt thereof inhibits a matrix metalloprotease *in situ*.

11. A method for preparing the conjugate of claim 1 comprising binding a site of the therapeutic agent for joint diseases that does not affect the activity of the agent to a



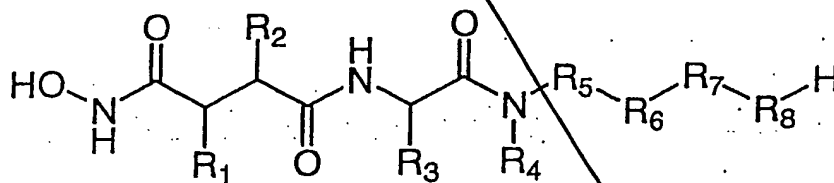
B3  
carboxyl group, a hydroxyl group or a functional group at the reducing end of hyaluronic acid, a hyaluronic acid derivative or a salt thereof by direct chemical reaction or via a spacer.

Delete the nonstatutory "use" claims 15 and 16 and insert therefor the following new claims:

--18. The conjugate of claim 1, wherein the therapeutic agent for joint diseases is selected from the group consisting of a cyclooxygenase 2 inhibitor, an antirheumatic agent and a matrix metalloprotease inhibitor.

B4  
--19. The conjugate of claim 1, wherein the bond between at least one therapeutic agent for joint diseases and hyaluronic acid, a hyaluronic acid derivative or a salt thereof is selected from the group consisting of an amide bond, an ether bond and a sulfide bond.

--20. A conjugate obtained by reacting a compound represented by the following general formula:



wherein



*BH*  
~~R<sub>1</sub> is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;~~

~~R<sub>2</sub> is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;~~

~~R<sub>3</sub> is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group;~~

~~R<sub>4</sub> is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;~~

~~R<sub>5</sub> is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;~~

~~R<sub>6</sub> is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;~~

~~R<sub>7</sub> is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and~~

~~R<sub>8</sub> is an oxygen atom, a sulfur atom or NR<sub>9</sub> wherein R<sub>9</sub> is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;~~

with a hyaluronic acid derivative or a salt thereof and a dehydrative condensation agent.



1. A conjugate according to claim 1, wherein the compound represented by the following formula is a hydrogen atom, a hydroxyl group, a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms, an aryl group or a substituted aryl group, an alkyl group having 1 to 8 carbon atoms, a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms, an oxygen atom or a methylene group, or a group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}_1 - \text{CH} - \text{CH}(\text{R}_2) - \text{C}(=\text{O}) - \text{NH} - \text{CH}(\text{R}_3) - \text{C}(=\text{O}) - \text{N}(\text{R}_4) - \text{R}_5 - \text{R}_6 - \text{R}_7 \end{array}$$

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub> are defined as above.



$R_1$  is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

~~R<sub>3</sub> is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group;~~

R<sub>5</sub> is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;

R<sub>6</sub> is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;



*By*  
R<sub>7</sub> is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and  
R<sub>8</sub> is an oxygen atom, a sulfur atom or NR<sub>9</sub> wherein R<sub>9</sub> is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;  
with a hyaluronic acid derivative or a salt thereof, a dehydrative condensation agent and a reaction accelerating additive.

--22. In a method of treating a joint disease in a patient in need thereof, comprising administering a pharmaceutical composition to said patient in an amount sufficient for said treatment, the improvement wherein said pharmaceutical composition comprises a conjugate in accordance with claim 4.--

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REMARKS

Amendments presented above in claims 1, 2, 4, 10 and 11 correct the misspelling of hyaluronic acid. In addition, claim dependencies have been amended to provide better antecedent basis.

The formulas submitted in new claims 20 and 21 depict compounds obtained by binding a compound of Formula (1) and a compound of Formula (2). Compounds satisfying this new formula are disclosed as compounds 3, 4, 6, 7 and 9 in example 1 of the present specification.